

REMARKS

Further and favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Claims 1-15 were cancelled and claims 16-22 were previously added in the Amendment filed May 22, 2009. By this Amendment, claims 16, 17, 19 and 22 are amended, and claim 23 is added.

Support for amended claim 16 can be found at page 7, lines 10-11, page 8, lines 14-27, page 10, lines 11-25, Example 2, page 20, line 4 – page 21, line 27, and Tables 2 and 3 of the specification.

Claim 17 is amended to make minor editorial changes that are self-explanatory.

Support for amended claim 19 can be found at page 7, lines 10-11, page 8, lines 14-27, page 10, lines 6-10, Example 1, page 17, line 18 – page 18, line 11, and Table 1 of the specification.

Support for amended claim 22 can be found at page 7, lines 10-11 and page 8, lines 14-22 of the specification.

Support for new claim 23 can be found in Example 1, Table 1, of the specification.

The amendments have been made in order to make it clear that in the claimed aseptic combination preparation, the same medicinal ingredient (e.g., the same potassium salt, the same sodium salt, the same sugar, etc.) is present in each of the two or more separate chambers. The basis of these amendments can be found on page 7, lines 10-11 and page 8, lines 14-16 of the specification.

For the Examiner's convenience, Applicants provide the following table explaining which medicinal ingredient is present in each of the separate chambers in the three Working Examples provided in the specification.

Working Example	The Same Medicinal Ingredient(s)
1	Sodium chloride
2	Dipotassium phosphate
3	Sodium chloride, Potassium chloride

I. Claim Rejection Under 35 U.S.C. § 102

The Examiner rejects claims 1, 2, 6-8 and 10-11 under 35 U.S.C. § 102(b) as being anticipated by Veech (U.S. 5,200,200). Claims 1, 2, 6-8 and 10-11 are cancelled, rendering the rejection moot. However, Applicants provide the following remarks regarding new claims 16, 19 and 22, and Veech.

Claim 16

Veech discloses a parenteral solution having a potassium ion concentration of 0-5 mM/Liter (0-5 mEq/L) in col. 6, lines 11-25, and a peritoneal dialysis solution having a potassium ion concentration of 0-5 mM/Liter (0-5 mEq/L) in col. 6, lines 26-40.

However, Veech does not specifically disclose the combination of the recited technical features in claim 16 of: (i) a **first solution containing a potassium salt in a first chamber and a second solution containing a potassium salt in a second chamber**, and (ii) the first solution and the second solution **each have the same potassium salt and each have a potassium ion concentration of about 2 to 40 mEq/L**.

Because Veech does not disclose each and every feature of claim 16, Veech does not anticipate claim 16.

Claim 19

Veech discloses in col. 6, lines 26-40 a peritoneal dialysis solution containing sodium ions, potassium ions and glucose (i.e., sugar). However, Veech does not specifically disclose the combination of the recited technical features of claim 19 of: (i) a **first solution containing at least one medicinal ingredient selected from the group consisting of a sodium salt, a sugar and a potassium salt in a first chamber, and a second solution containing at least one medicinal ingredient selected from the group consisting of a sodium salt, a sugar and a potassium salt in a second chamber**, and (ii) the first solution and the second solution **each has the same medicinal ingredient and each has an osmotic pressure ratio in the range of about 1 to 3 relative to physiological saline**.

In particular, “**an osmotic pressure ratio in the range of about 1 to 3 relative to physiological saline**” is not disclosed in Veech.

Therefore, claim 19 is not anticipated by Veech.

Claim 22

Veech discloses in EXAMPLE 1 (col. 7, lines 19-61) that a solution of crystalline sodium pyruvate is charged into chamber 12 of a container and thereafter a master batch solution containing a sodium ion, a potassium ion and glucose (col. 7, lines 24-34), is charged into chamber 11 of a container (col. 7, lines 36-45). **That is, in Veech, the same medicinal ingredient is not present in two chambers of one container.**

Thus, Veech does not disclose the recited technical feature in claim 22 that "**the same medicinal ingredient is present in each of the two chambers.**"

Therefore, claim 22 is not anticipated by Veech.

Because claims 16, 19 and 22 are not anticipated by Veech, and claims 17, 18, 20 and 21, and new claim 23, depend directly from claim 16 or 19, claims 17, 18, 20, 21 and 23 also are not anticipated by Veech.

II. Claim Rejection Under 35 U.S.C. § 103

The Examiner rejects claims 1, 3-5 and 12-14 under 35 U.S.C. § 103(a) as being unpatentable over Veech in view of Nakamura et al. (U.S. 6,867,193). By this Amendment, claims 1, 3-5 and 12-14 are cancelled, rendering the rejection moot. However, Applicants provide the following comments regarding claims 16-23 and the cited references.

(1) The Technical Features of the Present Invention

Claim 16

The combination of the recited technical features of claim 16 of: (i) **a first solution containing a potassium salt in a first chamber and a second solution containing a potassium salt in a second chamber, and (ii) the first solution and the second solution each have the same potassium salt and each have a potassium ion concentration of about 2 to 40 mEq/L** would not have been obvious from Veech in view of Nakamura to those of ordinary skill in the art.

Claim 19

Veech does not specifically disclose the combination of the recited technical features of claim 19 of: (i) **a first solution containing at least one medicinal ingredient** selected from the group consisting of a sodium salt, a sugar and a potassium salt in a first chamber, **and a second solution containing at least one medicinal ingredient** selected from the group consisting of a sodium salt, a sugar and a potassium salt in a second chamber, and (ii) the first solution and the second solution **each has the same medicinal ingredient and each has an osmotic pressure ratio in the range of about 1 to 3 relative to physiological saline.**

In particular, Veech does not teach “**an osmotic pressure ratio in the range of about 1 to 3 relative to physiological saline.**”

The Nakamura et al. reference discloses “**an osmotic pressure ratio of 2.8 to 3.3**” in PREPARATION EXAMPLES 1-3 (col. 4, line 65 - col. 6, line 29). However, these examples are liquid formulations in which the total components are dissolved in **one chamber**. Further, PREPARATION EXAMPLE 2 of Nakamura et al. consists of two solutions in a double bag. However, the reference describes in col. 5, lines 51-53, that “When used, the two solutions in the double bag were mixed. The drug solution **after they were mixed** had...an osmotic pressure ratio of 2.8 to 3.3” (emphasis added). Thus, the osmotic pressure ratio of 2.8 to 3.3 that is disclosed in Nakamura et al. is a value **after two solutions were mixed.**

In contrast, the preparation of claim 19 has the recited feature (ii) of: “**the first solution and the second solution each has the same medicinal ingredient and each has an osmotic pressure ratio in the range of about 1 to 3 relative to physiological saline.**” Nakamura et al. does not teach or suggest this claimed feature.

Therefore, Veech and Nakamura et al. do not teach or suggest each and every feature of claim 19. Accordingly, claim 19 would not have been rendered obvious by the references.

Claim 22

In Veech, the same medicinal ingredient is **not** present in the two chambers of a container, as discussed above. The Nakamura et al. reference discloses in col. 4, lines 26-27 that “**separate components may be filled into both upper and lower ones of two chambers**” (emphasis added). The reference further discloses in col. 4, lines 32 - 35 that “**The lower chamber of this**

bag is filled with a solution containing amino acids and the upper chamber is filled with a powder, a solid or a solution comprising albumin". That is, in Nakamura et al., the same medicinal ingredient is not present in two chambers of one container, which is similar to Veech.

Thus, the recited technical feature in claim 22 of "**the same medicinal ingredient is present in each of the two chambers**" would not have been obvious over Veech in view of Nakamura et al. to those skilled in the art.

(2) The Unexpected Effects of the Present Invention

As presented by Applicants in the Amendment filed May 22, 2009, the present invention provides unexpected results over the prior art. For the Examiner's convenience, Applicants reiterate the remarks below.

Various Medicinal Ingredients Contained in the Infusion

Intravenous infusion is applied to a patient who cannot have oral nutritional support. Such an infusion is usually a solution which contains various medicinal ingredients. For example, an infusion solution contains medicinal ingredients including a sugar, such as glucose, an amino acid, an electrolyte, such as a potassium salt (e.g., potassium chloride and potassium bicarbonate), a sodium salt (e.g., sodium chloride and sodium bicarbonate), a calcium salt (e.g., calcium chloride) and a magnesium salt (e.g., magnesium chloride), a vitamin (e.g., vitamin C and vitamin E) and a fatty acid. **The potassium salt, the sodium salt and the sugar are the important ingredients.**

Possible Reaction Between Medicinal Ingredients During Storage of the Infusion

It is rare that such an infusion is administered to a patient as soon as the infusion is produced. Such an infusion must be preserved for months in, for example, a hospital warehouse, because the infusion is produced in a factory, and then transported to a hospital where it is stored, and ultimately administered to a patient.

When a potassium salt (i.e., potassium bicarbonate) and magnesium salt (or calcium salt) as medicinal ingredients are contained in an infusion as a solution, potassium bicarbonate reacts with magnesium chloride to produce a precipitate (i.e., magnesium carbonate) in the

infusion during the storage of the infusion, thereby making intravenous administration of the infusion to a patient impossible.

A similar undesirable reaction can occur between a sodium salt (i.e., sodium bicarbonate) and magnesium chloride (or calcium chloride) during the storage of an infusion. A similar undesirable reaction can also occur between a sugar and an amino acid. When a solution containing an amino acid and a sugar together is preserved for a few months, the solution becomes brown because of a Maillard reaction between the sugar and the amino acid, thereby causing a brown colored infusion, and a loss of commercial value.

Separation of Reactive Medicinal Ingredients by Using Two or More Chambers

The above-mentioned problem of generating a precipitate (i.e., magnesium carbonate) can be avoided. For example, two chambers are formed in one container and divided by a partition wall (see Fig. 1 of the present application). A solution containing potassium bicarbonate and a solution containing magnesium chloride are separately accommodated and preserved in each chamber until the time of administration of the infusion into the patient. Then, the two solutions are mixed by communicating the two chambers just before administration, and the obtained infusion which contains potassium bicarbonate and magnesium carbonate can be administered to a patient before any magnesium carbonate precipitates. A similar separation can also be made with regard to a sodium salt or a sugar.

Concentration of the Medicinal Ingredients and Osmotic Pressure of the Infusion

The solutions containing medicinal ingredients are separately preserved in different chambers with each other to avoid an undesirable reaction. The chambers are communicated by removing the partition wall in order to mix all the solutions in the chambers, thereby obtaining an infusion with suitable concentrations of ingredients and osmotic pressure, which can be administered to a patient.

It is common in the art that each of the solutions of the plurality of chambers have different concentrations of ingredients and osmotic pressure ratios relative to physiological saline. It is also common for some of the concentrations and/or osmotic pressure ratios to be dangerous and outside of a range that is safe for a patient. Moreover, the dangerous

concentrations and osmotic pressure ratios are usually adjusted into a range that is safe to a patient by combining the solutions in the plurality of chambers by communicating the chambers, and removing the partition walls. The distribution of the ingredients into the chambers is arranged so that the above function can work properly and safely.

Operation Mistakes

In the medical field, various operation mistakes by doctors and nurses frequently occur. Regarding the infusion, at times the above-mentioned communication of the plurality of chambers in the container is not properly made by the doctor or nurse, and only one of the solutions among the solutions accommodated in the chambers is erroneously administered to a patient.

Hyperkalemia Is Highly Dangerous to Patients

As apparent from the above-mentioned explanation, the erroneous administration of a potassium salt solution to a patient without communicating all of the chambers in the container can create a concentration of potassium ions that is too high. If the potassium ion concentration is excessively high, then the potassium ion concentration in the blood of the patient will be excessively high, and result in hyperkalemia, and/or, in the worst case, death by cardiac arrest. These are serious consequences known in the art that can result from these defects.

Severe Vessel Pain and Destruction of Erythrocytes in the Blood

When an **osmotic pressure ratio** of a solution in one chamber among a plurality of chambers is excessively high or low relative to a physiological saline, then the plurality of the chambers is not properly communicated, and it can result in administering to a patient a solution having an excessively high or low osmotic pressure ratio relative to a physiological saline. This will cause serious conditions in the patient because of severe vessel pain and destruction of erythrocytes in the blood. This is a serious problem in the medical field. These accidents could happen when other medicinal ingredients, such as a sodium salt and a sugar, are used.

The Remarkable and Unexpected Effect of the Present Invention

Fortunately, the claimed invention solves the above-mentioned problems, and can eliminate any adverse effects on a living body caused by medical mistakes.

As a result of intensive studies of the above-mentioned problems, the present inventors have found that a preparation to be mixed aseptically **at the time of use** has been successfully produced. Thus, the present inventors have found that the preparation can solve both of the above-mentioned problems caused by inadvertently failing to properly communicate the chambers in the known preparations.

The present inventors have succeeded in creating a new preparation in which the potassium ion concentration and osmotic pressure ratio to physiological saline of a solution containing at least one medicinal ingredient selected from the group consisting of a sodium salt, a sugar and a potassium salt, accommodated in a plurality of chambers, are adjusted in a proper range (i.e., a potassium ion concentration in the solution of about 2 to 40 mEq/L, and an osmotic pressure ratio of the solution in the range of about 1 to 3 relative to physiological saline) (**claims 16 and 19**). The present inventors have unexpectedly found that there is no risk of causing hemolysis due to low osmotic pressure, or hyperkalemia due to a high concentration of potassium ions, etc. with the claimed invention. The claimed preparation can prevent adverse effects on a living body by medical mistakes even if the medicinal ingredients-containing solution in only one chamber is administered to a patient by mistake. This is a remarkably excellent effect, which would not have been obvious to those skilled in the art from the disclosures of Veech and Nakamura et al.

Accordingly, claims 16, 19 and 22 would not have been rendered obvious by Veech in view of Nakamura et al. Claims 17, 18, 20, 21 and 23 depend directly from claim 16 or 19, and thus also would not have been rendered obvious by the references.

III. Conclusion

For these reasons, Applicants take the position that the presently claimed invention is clearly patentable over the applied references. Therefore, in view of the foregoing amendments and remarks, it is submitted that the rejections set forth by the Examiner have been overcome, and that the application is in condition for allowance. Such allowance is solicited.

Respectfully submitted,

Nobuaki SUMIYOSHI et al.

By: 
Andrew B. Freistein
Registration No. 52,917
Attorney for Applicants

WMC/ABF/rgf
Washington, D.C. 20005-1503
Telephone (202) 721-8200
Facsimile (202) 721-8250
July 23, 2009